## REMARKS

Provisional Rejection of Claims 1-4 and 6-22 under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1-4 and 6-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable "over claims 1-24 of co-pending Application No. 09/442,979" (Office Action, page 2).

As the Examiner notes, Applicants will address the provisional rejection upon indication that there is allowable subject matter in the referenced application.

Rejection of Claim 1-4, 6-9, 15-19, 21 and 22 under 35 U.S.C. §103(a)

Claims 1-4, 6-9, 15-19, 21 and 22 are rejected under 35 U.S.C. §103(a) as being unpatentable over Tai *et al.* and Merten *et al.* in view of Wei *et al.* (Office Action, page 3). The Examiner states that Tai *et al.* "clearly teaches that appropriate semipermeability is required that allow easy diffusion of secreted gene product without compromising the immunoisolating properties of the membrane" (Office Action, page 4). The Examiner further states that Merten *et al.* teach "an encapsulation method which result in the retention of a secreted product while allowing the survival of encapsulated cells in a growth media" and "retention and release of secreted products by selecting a retention or product releasing capsule system" (Office Action, page 4). The Examiner cites Wei *et al.* as teaching "genetically engineered mouse fibroblasts that produce Cytochrome P450, wherein the P450 activates an inert prodrug like CPA into cytotoxic metabolites" (Office Action, page 4). The Examiner concludes that:

> it would have been obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Tai and Merten who teaches the encapsulation of genetically engineered cells with selected membrane permeability, with the teaching of Wei who teaches genetically engineered cells that produces p450 which activates an inert prodrug. One would have been motivated to encapsulate the cytochrome p450 producing cells in order to retain the P450 gene product within the capsule (Marten)) [sic] or to avoid immune rejection (Tai). One would have a reasonable expectation of success because prior art clearly teaches that manipulation of pore size of capsule membrane is well within the reach of one of ordinary skill in the art (Office Action, pages 4-5).

Applicants respectfully disagree. The cited art does not teach or suggest encapsulation of cells which produce a ***non-secreted protein***. Furthermore, the cited art does not teach or suggest

manipulating the pore size of a capsule to allow entry of an inactive prodrug and release of the active form of the prodrug.

Applicants' claimed invention is directed to encapsulation of cells which do not produce a secreted product. As pointed out in the previously filed Amendment mailed to the U.S. Patent Office on July 18, 2000, ***cytochrome P450*** is not a secreted protein. Rather it is a ***membrane-bound enzyme that functions when integrated into the membrane of cells*** and is not able to leave the transduced cells. Thus, the cytochrome P450 cannot pass out of or be delivered from Applicants' claimed capsule. According to Applicants' invention, the expressed cytochrome P450 protein integrates into the membrane of the encapsulated cells, and the encapsulated cells are injected or transplanted into or at the site of a tumor. A prodrug (*e.g.,* ifosfamide) is administered, wherein the prodrug enters the capsule and is converted into its active form by the cytochrome P450. Subsequently, the activated drug is delivered from the capsules and directly attacks the tumor.

The art teaches that the pore size of the capsule can be manipulated to either retain or secrete a ***protein secreted from an encapsulated cell*** (e.g., a hybridoma which secretes IgG or IgM (Merten et al.), fibroblasts which secrete human growth hormone (Tai et al.)). The Examiner cites Merten *et al.* for their teaching of "an encapsulation method which results in the retention of a secreted product" (Office Action, page 4).

> Merten *et al.* clearly teach that:
>
> it is possible to choose between a complete ***product (IgG and IgM*** (data not shown)) ***retention*** or a ***product releasing*** capsule system (Merten *et al.*, page 128, column 2, emphasis added).

However, Merten *et al.* describe an encapsulation system "which was developed for the ***cultivation of mammalian cells***" (Merten *et al.*, abstract, emphasis added). Specifically, Merten *et al.* tested and optimized an encapsulation system which "***enables retention of cells in bioreactor systems*** allowing higher product titers and volumetric productivities due to higher cell densities" (Merten *et al.*, page 121, columns 1-2, emphasis added). Thus, when Merten *et al.* refers to retention of a product produced in a capsule, it is in the context of a ***mammalian cell culture system*** in which the retained product is harvested from the capsules, not in the context of ***delivering the expressed product of a gene in vivo***.

Clearly, based on the art at the time of Applicants' invention, a person of skill in the art would not be motivated to encapsulate the genetically engineered mouse fibroblasts that produce cytochrome P450, a ***membrane-bound enzyme that functions when integrated into the membrane of cells to convert a chemotherapeutic prodrug into its active state*** of Wei *et al.*, because the cytochrome P450 would be unable to leave the capsule. As a result, one of skill in the art would expect that the cytochrome P450 would not be able to convert a prodrug (*e.g.*, cyclophosphamide or ifosfamide) that had been administered systemically, at the site of the implanted capsules

It is equally clear that the art at the time of Applicants' invention does not teach or even suggest manipulating the pore size of a capsule to allow ***entry*** of an inactive prodrug wherein the prodrug becomes active in the cell, ***and then release*** of the active form of the prodrug. Indeed, the cited art teaches away from manipulating the pore size of the capsule to allow ***entry of components outside the capsule into the capsule***. For example, Tai *et al.* teach that "an important feature of the microencapsulation technique" is that it "isolates the genetically modified cells from the recipient's immune system" (Tai *et al.*, page 1068, column 1). Tai *et al.* further states that:

> the development of the appropriate APA membrane for the ***purpose of implantation*** clearly indicates that it can provide free passage of the recombinant products while ***maintaining the immunoisolating properties of the membrane*** (Tai *et al.*, page 1067, column 1, emphasis added).

Clearly, a person of skill in the art would not be motivated to encapsulate the genetically engineered mouse fibroblasts that produce cytochrome P450 of the Wei *et al.* reference.

Applicants maintain that the prior art combination of record has been made with the advantage of *impermissible hindsight*, and thus, the rejection is legally improper. That is, the obviousness rejection has been made with knowledge gleaned only from Applicants' disclosure in which there is a clear teaching of a capsule comprising a porous membrane formed by a polyelectrolyte complex which encapsulates cells which express a cytochrome P450 gene, wherein the membrane is permeable to prodrug molecules and the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule. In the present case, the

suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The combined teachings of Tai *et al.*, Wei *et al.* and Merten *et al.* do not render obvious Applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

## CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Concord, MA 01742-9133
Dated: November 24, 2003